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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,844	01/26/2006	Jadwiga Bienkowska	ARS-110	2201

23557 7590 09/17/2008

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
09/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,844	BIENKOWSKA ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Revised Notice; PTO-90C*.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 24 June 2008 and 27 June 2005 have been entered in full. Claims 1-56 are cancelled. Claims 57-80 are added.

Election/Restrictions

Applicant's election without traverse of Group I, claims 42-44, 47, 48-50 in the reply filed on 24 June 2008 is acknowledged.

Claims 57-80 are under consideration in the instant application.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). **Specifically, the sequences disclosed in Figures 1 and 2 are not accompanied by the required reference to the relevant sequence identifiers.** This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). Please also see the enclosed Revised Notice to Comply and PTO-90C.

Specification

1. The disclosure is objected to because of the following informalities:

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "NOTCH-LIKE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE POLYPEPTIDES".

Appropriate correction is required.

Claim Objections

3. Claim 80 is objected to because of the following informalities:

4. In claim 80, line 1 a word is missing after the term "comprising".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 57-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. The term "notch-like activity" in claims 57-80 is a relative term which renders the claims indefinite. The term "notch-like activity" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is well known in the art that Notch proteins have many different activities (see for instance, specification page 2, lines 3-29). However, the specification does not define "notch-like activity" and hence, the skilled artisan would not know how to identify the claimed polypeptides of the instant invention.

Claim Rejections - 35 USC § 101 and 35 U.S.C. § 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 57-80 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.

The claims are directed to an isolated polypeptide comprising (a) SEQ ID NO: 2; (b) SEQ ID NO: 4; (c) an amino acid sequence having at least 85% identity to SEQ ID NO: 2 or 4 and having notch-like activity; (d) a fusion protein comprising a heterologous sequence and a polypeptide set forth in (a) or (b) or (c); or a polypeptide as set forth in (a) or (b) or (c) or (d), wherein said polypeptide further comprises radioactive labels, fluorescent labels, biotin, or cytotoxic agents. The claims are also directed to nucleic acid molecules that encode such polypeptides. Claim 79 recites a vector comprising the nucleic acid. Claim 80 recites an isolated host cell comprising the nucleic acid.

The specification of the instant application discloses that "[t]he invention is based upon the identification of an Open Reading Frame (ORF) in the human genome encoding a novel notch-like polypeptide" (page 3, lines 4-6). However, the instant specification does not teach any significance or functional characteristics of the SCS0006 notch-like polypeptides (SEQ ID NO: 2, SEQ ID NO: 4) or nucleic acid molecules (SEQ ID NO: 1, SEQ ID NO: 3). The specification also does not disclose any methods or working examples that indicate the polypeptides and nucleic acids of the instant invention are involved in any activity. There is no

biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with SCS0006. Without any information as to the specific properties of SCS0006, the mere identification of the polypeptide is not sufficient to impart any particular utility to the claimed polypeptides and nucleic acids. Since significant further research would be required of the skilled artisan to determine how the claimed polypeptides and nucleic acids are involved in any activities, the asserted utilities are not substantial. Since the utility is not presented in mature form and significant further research is required, the utility is not substantial. The specification asserts the following as patentable utilities for the claimed putative polypeptides (SEQ ID NO: 2, SEQ ID NO: 4) and nucleic acids (SEQ ID NO: 1, SEQ ID NO: 3):

1) to produce a variant polypeptide (page 10, lines 6-30 through page 17)

2) to screen for compounds that enhance or reduce expression level of the polypeptide or nucleic acid (page 22, lines 1-4)

3) to produce antibodies against the polypeptide (page 15, lines 1-10)

4) to treat diseases and conditions in which the notch-like polypeptide is implicated (page 6, lines 27-29; page 7, lines 1-7; page 8, lines 18-30; page 9, lines 1-3)

5) to diagnose disease in a patient (page 7, lines 8-27)

6) to generate transgenic or "knock out" animals (page 9, lines 4-9)

Each of these shall be addressed in turn.

1) to produce a variant polypeptide. This asserted utility is not specific or substantial. Such assays can be performed with any polypeptide. Further, the specification discloses nothing specific or substantial for the variant polypeptide that is produced by this method. Since this

asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

2) to screen for compounds that enhance or reduce expression level of the polypeptide or nucleic acid. This asserted utility is not specific or substantial. Such assays can be performed with any polypeptide or nucleic acid. Additionally, the specification discloses nothing specific or substantial for the compounds that can be identified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) to produce antibodies against the polypeptide. This asserted utility is not specific or substantial. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, therefore both the polypeptide and its antibodies have no patentable utility. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) treat diseases and conditions in which the notch-like polypeptide is implicated. This asserted utility is not specific or substantial. The specification does not disclose which cells or tissues are to be targeted or which diseases or diseases are to be treated. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease or condition. The specification also does not disclose if the cells, tissues, or disorders are associated with altered levels or forms of the SCS0006 polypeptide or nucleic acid. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

5) to diagnose disease in a patient. This asserted utility not specific or substantial. Such assays can be performed with any polypeptide or nucleic acid. Further, the specification does not disclose the tissues or cell types the polypeptide or nucleic acid is normally expressed in. The specification also discloses nothing about the normal levels of expression of the polypeptide or nucleic acid or a specific DNA target. The specification does not disclose diseases associated with a SCS0006 polypeptide or nucleic acid. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

6) to generate transgenic or "knock out" animals. This asserted utility is not specific or substantial. The specification does not disclose diseases associated with a mutated, deleted, or translocated SCS0006 gene (SEQ ID NOs: 1, 3). Significant further experimentation would be required of the skilled artisan to identify such a disease. The specification discloses nothing about whether the gene will be "knocked in" or "knocked out" or what specific tissues and cells are being targeted. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

8. Claims 57-80 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 57, 60-61, 64-68, 71-72, and

75-80 would remain rejected under 35 U.S.C. § 112, first paragraph. Specifically, the specification teaches that the invention includes variants of the amino acid sequence recited in SEQ ID NO: 2 or SEQ ID NO: 4, wherein any amino acid specified in the chosen sequence is non-conservatively substituted, provided that no more than 15%, preferably no more than 10%, 5%, 3%, or 1% of the amino acid residues in the sequence are so changed" (page 10, lines 6-9 and lines 22-27). However, the specification does not teach any variant, fragment, or derivative of the SCS0006 polypeptide and nucleic acid other than the full-length amino acid sequences of SEQ ID NO: 2 and 4 and the full-length nucleic acid sequences of SEQ ID NOs: 1 and 3. The specification also does not teach functional or structural characteristics of the polypeptide variants, fragments, and derivatives (including the extracellular domain) recited in the claims.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to

enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

10. Claims 57, 60-61, 64-68, 71-72, and 75-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an isolated polypeptide comprising (a) SEQ ID NO: 2; (b) SEQ ID NO: 4; (c) an amino acid sequence having at least 85% identity to SEQ ID NO: 2 or 4 and having notch-like activity; (d) a fusion protein comprising a heterologous sequence and a polypeptide set forth in (a) or (b) or (c); or a polypeptide as set forth in (a) or (b) or (c) or (d), wherein said polypeptide further comprises radioactive labels, fluorescent labels, biotin, or cytotoxic agents. The claims are also directed to nucleic acid molecules that encode such polypeptides. Claim 79 recites a vector comprising the nucleic acid. Claim 80 recites an isolated host cell comprising the nucleic acid.

The specification teaches that the instant invention includes variants of the amino acid sequence recited in SEQ ID NO: 2 or SEQ ID NO: 4, wherein any amino acid specified in the chosen sequence is non-conservatively substituted, provided that no more than 15%, preferably no more than 10%, 5%, 3%, or 1% of the amino acid residues in the sequence are so changed" (page 10, lines 6-9 and lines 22-27). The claims of the instant application do not require that the polypeptide variants possess any particular conserved structure or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides and nucleic acids encoding such. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The

factors to be considered include actual reduction to practice, disclosure of drawings or structure chemical formulas, sufficient relevant identifying characteristics (such as, complete or partial structure, physical and/or chemical properties, and functional characteristics when coupled with a known or disclosed structure/function correlation), methods of making the claimed product, level of skill and knowledge in the art, predictability in the art, or any combination thereof. However, in this case, the specification fails to disclose and there is no art-recognized correlation between the structure of the genus of claimed polypeptides (and nucleic acids) and their function of notch-like activity. The specification does not teach which 15% of the amino acids can vary from SEQ ID NOs: 2 and 4 and still result in a protein that retains notch-like activity. The specification also does not teach which nucleic acids that encode a polypeptide with at least 85% sequence identity to SEQ ID NO: 2 or 4 encode a polypeptide having the required notch-like activity. Therefore, the description of two notch-like polypeptides (SEQ ID NOs: 2, 4) and nucleic acids encoding such (SEQ ID NOs: 1, 3) is not adequate written description of an entire genus of functionally equivalent polypeptides and nucleic acids having notch-like activity.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

Thus, the skilled artisan cannot envision the detailed chemical structure of the polypeptide and nucleic acid variants of the encompassed claims, and therefore conception is not

achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The polypeptides and nucleic acid molecules are required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and nucleic acid molecules encoding such, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 57, 60-61, 64-68, 71-72, and 75-80 are rejected under 35 U.S.C. 102(e) as being anticipated by Karim et al. (US20030100005; priority to 26 November 2001).

Karim et al. teach an isolated CRUMBS (CRB) protein that is 98% identical to the amino acid sequence of SEQ ID NO: 2 and 99% identical to the amino acid sequence of SEQ ID NO: 4 of the instant application (see SEQ ID NO: 17 of Karim et al.; also, see sequence alignments attached to the instant Office Action as Appendices A and B, respectively). Karim et al. disclose an isolated nucleic acid encoding a polypeptide that is at least 85% identical to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4 (see SEQ ID NO: 8 of Karim et al.; see sequence alignments attached to the instant Office Action as Appendices C and D, respectively). Karim et al. also teach that the nucleotide sequence encoding a CRB polypeptide can be inserted into any appropriate expression vector (page 4, [0032-0033]). Karim et al. teach an isolated host cell comprising the CRB nucleic acid/vector (page 4, [0032]).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
10 September 2008

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

Appendix A
SEQ ID NO: 2

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US-10-303-685-17
; Sequence 17, Application US/10303685
; Publication No. US20030100005A1
; GENERAL INFORMATION:
;  APPLICANT: Exelixis, Inc.
;  TITLE OF INVENTION: CRBs AS MODIFIERS OF BRANCHING MORPHOGENESIS AND METHODS OF US
;  FILE REFERENCE: EX02-125C
;  CURRENT APPLICATION NUMBER: US/10/303,685
;  CURRENT FILING DATE:  2002-11-25
;  PRIOR APPLICATION NUMBER: 60/333,388
;  PRIOR FILING DATE: 2001-11-26
;  NUMBER OF SEQ ID NOS: 17
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 17
;   LENGTH: 1307
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-10-303-685-17

  Query Match             98.04%;  Score 6765.5;  DB 4;  Length 1307;
  Best Local Similarity   93.4%;  Pred. No. 0;
  Matches 1221;  Conservative    0;  Mismatches    3;  Indels   83;  Gaps    3;

Qy          13 MALARPGTPDPQALASVLLLLLWAPALSLLA----------------------GTVPSEP 50
               |||||||||||||||||||||||||||||||                      |||||||
Db           1 MALARPGTPDPQALASVLLLLLWAPALSLLAGGNSLELCSEPKLSRVGQCQAQGTVPSEP 60

Qy          51 PSACASDPCAPGTECQATESGGYTCGPMEPRGCATQPCHHGALCVPQGPDPNGFRCYCVP 110
               |||||||||||||||||||||||||||||||||||||||||||||||||| ||||||||
Db          61 PSACASDPCAPGTECQATESGGYTCGPMEPRGCATQPCHHGALCVPQGPDPTGFRCYCVP 120

Qy         111 GFQGPRCELDIDECASRPCHHGATCRNLADRYECHCPLGYAGVTCEHEVDECASAPCLHG 170
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         121 GFQGPRCELDIDECASRPCHHGATCRNLADRYECHCPLGYAGVTCEHEVDECASAPCLHG 180

Qy         171 GSCLDGVGSFRCVCAPGYGGTRCQLDLDECQSQPCAHGGTCHDLVNGFRCDCAGTGYEGT 230
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         181 GSCLDGVGSFRCVCAPGYGGTRCQLDLDECQSQPCAHGGTCHDLVNGFRCDCAGTGYEGT 240

Qy         231 HCEREVLECASAPCEHNASCLEGLGSFRCLCWPGYSGELCEVDEDECASSPCQHGGRCLQ 290
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         241 HCEREVLECASAPCEHNASCLEGLGSFRCLCWPGYSGELCEVDEDECASSPCQHGGRCLQ 300

Qy         291 RSDPALYGGVQAAFPGAFSFRHAAGFLCHCPPGFE------------------------- 325
               |||||||||||||||||||||||||||||||||
Db         301 RSDPALYGGVQAAFPGAFSFRHAAGFLCHCPPGFEGADCGVEVDECASRPCLNGGHCQDL 360

Qy         326 -------------GPTCEEDVDECLSDPCLHGGTCSDTVAGYICRCPETWGGRDCSVQLT 372
                           ||||||||||||||||||||||||||||||||||||||||||||||||
Db         361 PNGFQCHCPDGYAGPTCEEDVDECLSDPCLHGGTCSDTVAGYICRCPETWGGRDCSVQLT 420

Qy         373 GCQGHTCPLAATCIPIFESGVHSYVCHCPPGTHGPFCGQNTTFSVMAGSPIQASVPAGGP 432
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         421 GCQGHTCPLAATCIPIFESGVHSYVCHCPPGTHGPFCGQNTTFSVMAGSPIQASVPAGGP 480
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Qy        433 LGLALRFRTTLPAGTLATRNDTKESLELALVAATLQATLWSYSTTVLVLRLPDLALNDGH 492
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 LGLALRFRTTLPAGTLATRNDTKESLELALVAATLQATLWSYSTTVLVLRLPDLALNDGH 540

Qy        493 WHQVEVVLHLATLELRLWHEGCPARLCVASGPVALASTASATPLPAGISSAQLGDATFAG 552
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 WHQVEVVLHLATLELRLWHEGCPARLCVASGPVALASTASATPLPAGISSAQLGDATFAG 600

Qy        553 CLQDVRVDGHLLLPEDLGENVLLGCERREQCRPLPCVHGGSCVDLWTHFRCDCARPHRGP 612
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 CLQDVRVDGHLLLPEDLGENVLLGCERREQCRPLPCVHGGSCVDLWTHFRCDCARPHRGP 660

Qy        613 TCADEIPAATFGLGGAPSSASFLLQELPGPNLTVSFLLRTRESAGLLLQFANDSAAGLTV 672
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 TCADEIPAATFGLGGAPSSASFLLQELPGPNLTVSFLLRTRESAGLLLQFANDSAAGLTV 720

Qy        673 FLSEGRIRAEAPGSPAVVLPGRWDDGLRHLVMLSFGPDQLQDLGQHVHVGGRLLAADSQP 732
              |||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 FLSEGRIRAEVPGSPAVVLPGRWDDGLRHLVMLSFGPDQLQDLGQHVHVGGRLLAADSQP 780

Qy        733 WGGPFRGCLQDLRLDGCHLPFFPLPLDNSSQPSELGGRQSWNLTAGCVSEDMCSPDPCFN 792
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        781 WGGPFRGCLQDLRLDGCHLPFFPLPLDNSSQPSELGGRQSWNLTAGCVSEDMCSPDPCFN 840

Qy        793 GGTCLVTVNDFHCTCPANFTGPTCAQQLWCPGQPCLPPATCEEVPDGFVCVAEATFREGP 852
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 GGTCLVTVNDFHCTCPANFTGPTCAQQLWCPGQPCLPPATCEEVPDGFVCVAEATFREGP 900

Qy        853 PAAFSGHNASSGRLLGGLSLAFRTRDSEAWLLRAAAGALEGVULAVRNGSLAGGVRGGHG 912
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 PAAFSGHNASSGRLLGGLSLAFRTRDSEAWLLRAAAGALEGVULAVRNGSLAGGVRGGHG 960

Qy        913 LPGAVLPIPGPRVADGAWHRVRLAMERPAAATSRWLLWLDGAATPVALRGLASDLGFLQG 972
              |||||||||||||||||||||||||||| ||||||||||||||||||||||||||||||||
Db        961 LPGAVLPIPGPRVADGAWHRVRLAMERPAATTSRWLLWLDGAATPVALRGLASDLGFLQG 1020

Qy        973 PGAVRILLAENFTGCLGR-------------------------HFASWPGTPAPILGCRGAP 1009
              ||||||||||||||||                         ||||||||||||||||||
Db       1021 PGAVRILLAENFTGCLGRVALGGLPLPLARPRPGAAPGAREHFASWPGTPAPILGCRGAP 1080

Qy       1010 VCAPSPCLHDGACRDLFDAFACACGPGWEGPRCEAHVDPCHSAPCARGRCHTHPDGRFEC 1069
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1081 VCAPSPCLHDGACRDLFDAFACACGPGWEGPRCEAHVDPCHSAPCARGRCHTHPDGRFEC 1140

Qy       1070 RCPPGFGGPRCRLPVPSKECSLNVTCLDGSPCEGGSPAANCSCLEGLAGQRCQVPTLPCE 1129
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1141 RCPPGFGGPRCRLPVPSKECSLNVTCLDGSPCEGGSPAANCSCLEGLAGQRCQVPTLPCE 1200

Qy       1130 ANPCLNGGTCRAAGGVSECICNARFSGQFCEVAKGLPLPLFPFLLEVAVPAACACLLLLL 1189
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1201 ANPCLNGGTCRAAGGVSECICNARFSGQFCEVAKGLPLPLFPFLLEVAVPAACACLLLLL 1260

Qy       1190 LGLLSGILAARKRRQSEGTVSPSQQEVAGARLEMDSVLKVPPEERLI 1236
              ||||||||||||||||||||||||||||||||||||||||||||||||
Db       1261 LGLLSGILAARKRRQSEGTVSPSQQEVAGARLEMDSVLKVPPEERLI 1307
```

Appendix B
SEQ ID NO: 4

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RESULT 3
US-10-303-685-17
; Sequence 17, Application US/10303685
; Publication No. US20030100005A1
; GENERAL INFORMATION:
;  APPLICANT: Exelixis, Inc.
;  TITLE OF INVENTION: CRBs AS MODIFIERS OF BRANCHING MORPHOGENESIS AND METHODS OF USE
;  FILE REFERENCE: EX02-12SC
;  CURRENT APPLICATION NUMBER: US/10/303,685
;  CURRENT FILING DATE:  2002-11-25
;  PRIOR APPLICATION NUMBER: 60/333,388
;  PRIOR FILING DATE: 2001-11-26
;  NUMBER OF SEQ ID NOS: 17
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 17
;   LENGTH: 1307
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-10-303-685-17

  Query Match             99.0%;  Score 6613.5;  DB 4;  Length 1307;
  Best Local Similarity   94.9%;  Pred. No. 0;
  Matches 1186;  Conservative    0;  Mismatches    3;  Indels   61;  Gaps    2;

Qy          1 SEPPSACASDPCAPGTECQATESGGYTCGPMEPRGCATQPCHHGALCVPQGPDPNGFRCY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||| |||||
Db         58 SEPPSACASDPCAPGTECQATESGGYTCGPMEPRGCATQPCHHGALCVPQGPDPTGFRCY 117

Qy         61 CVPGFQGPRCELDIDECASRPCHHGATCRNLADRYECHCPLGYAGVTCEMEVDECASAPC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        118 CVPGFQGPRCELDIDECASRPCHHGATCRNLADRYECHCPLGYAGVTCEMEVDECASAPC 177

Qy        121 LHGGSCLDGVGSFRCVCAPGYGGTRCQLDLDECQSQPCAHGGTCHDLVNGFRCDCAGTGY 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        178 LHGGSCLDGVGSFRCVCAPGYGGTRCQLDLDECQSQPCAHGGTCHDLVNGFRCDCAGTGY 237

Qy        181 EGTHCEREVLECASAPCEHNASCLEGLGSFRCLCWPGYSGELCEVDEDECASSPCQHGGR 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        238 EGTHCEREVLECASAPCEHNASCLEGLGSFRCLCWPGYSGELCEVDEDECASSPCQHGGR 297

Qy        241 CLQRSDPALYGGVQAAFPGAFSFRHAAGFLCHCPPGFE---------------------- 278
              ||||||||||||||||||||||||||||||||||||||
Db        298 CLQRSDPALYGGVQAAFPGAFSFRHAAGFLCHCPPGFEGADCGVEVDECASRPCLNGGHC 357

Qy        279 ----------------GPTCEEDVDECLSDPCLHGGTCSDTVAGYICRCPETWGGRDCSV 322
                             ||||||||||||||||||||||||||||||||||||||||||||
Db        358 QDLPNGFQCHCPDGYAGPTCEEDVDECLSDPCLHGGTCSDTVAGYICRCPETWGGRDCSV 417

Qy        323 QLTGCQGHTCPLAATCIPIFESGVHSTVCHCPPGTHGPFCGQNTTFSVMAGSPIQASVPA 382
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        418 QLTGCQGHTCPLAATCIPIFESGVHSTVCHCPPGTHGPFCGQNTTFSVMAGSPIQASVPA 477
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Qy        383 GGPLGLALRFRTTLPAGTLATRNDTKESLELALVAATLQATLWSYSTTVLVLRLPDLALN 442
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        478 GGPLGLALRFRTTLPAGTLATRNDTKESLELALVAATLQATLWSYSTTVLVLRLPDLALN 537

Qy        443 DGHWHQVEVVLHLATLELRLWHEGCPARLCVASGPVALASTASATPLPAGISSAQLGDAT 502
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        538 DGHWHQVEVVLHLATLELRLWHEGCPARLCVASGPVALASTASATPLPAGISSAQLGDAT 597

Qy        503 FAGCLQDVRVDGHLLLPEDLGEMVLLGCERREQCRPLPCVHGGSCVDLWTHFRCDCARPH 562
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        598 FAGCLQDVRVDGHLLLPEDLGEMVLLGCERREQCRPLPCVHGGSCVDLWTHFRCDCARPH 657

Qy        563 RGPTCADEIPAATFGLGGAPSSASFLLQELPGPNLTVSFLLRTRESAGLLLQFANDSAAG 622
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        658 RGPTCADEIPAATFGLGGAPSSASFLLQELPGPNLTVSFLLRTRESAGLLLQFANDSAAG 717

Qy        623 LTVFLSEGRIRAEAPGSPAVVLPGRWDDGLRHLVMLSFGPDQLQDLGQHVHVGGRLLAAD 682
              |||||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db        718 LTVFLSEGRIRAEVPGSPAVVLPGRWDDGLRHLVMLSFGPDQLQDLGQHVHVGGRLLAAD 777

Qy        683 SQPWGGPFRGCLQDLRLDGCHLPFFPLPLDNSSQPSELGGRQSWNLTAGCVSEDMCSPDP 742
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        778 SQPWGGPFRGCLQDLRLDGCHLPFFPLPLDNSSQPSELGGRQSWNLTAGCVSEDMCSPDP 837

Qy        743 CFNGGTCLVTWNDFHCTCPANFTGPTCAQQLWCPGQPCLPPATCEEVPDGFVCVAEATFR 802
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        838 CFNGGTCLVTWNDFHCTCPANFTGPTCAQQLWCPGQPCLPPATCEEVPDGFVCVAEATFR 897

Qy        803 EGPPAAFSGHNASSGRLLGGLSLAFRTRDSEAWLLRAAAGALEGVWLAVRNGSLAGGVRG 862
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        898 EGPPAAFSGHNASSGRLLGGLSLAFRTRDSEAWLLRAAAGALEGVWLAVRNGSLAGGVRG 957

Qy        863 GHGLPGAVLPIPGPRVADGAWHRVRLAMERPAAATSRWLLWLDGAATPVALRGLASDLGF 922
              |||||||||||||||||||||||||||||| ||||||||||||||||||||||||||||||
Db        958 GHGLPGAVLPIPGPRVADGAWHRVRLAMERPAATTSRWLLWLDGAATPVALRGLASDLGF 1017

Qy        923 LQGPGAVRILLAENFTGCLGR----------------------HFASWPGTPAPILGCR 959
              |||||||||||||||||||||                      ||||||||||||||||
Db       1018 LQGPGAVRILLAENFTGCLGRVALGGLPLPLARPRPGAAPGAREHFASWPGTPAPILGCR 1077

Qy        960 GAPVCAPSPCLHDGACRDLFDAFACACGPGWEGPRCEAHVDPCHSAPCARGRCHTHPDGR 1019
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1078 GAPVCAPSPCLHDGACRDLFDAFACACGPGWEGPRCEAHVDPCHSAPCARGRCHTHPDGR 1137

Qy       1020 FECRCPPGFGGPRCRLPVPSKECSLNVTCLDGSPCEGGSPAANCSCLEGLAGQRCQVPTL 1079
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1138 FECRCPPGFGGPRCRLPVPSKECSLNVTCLDGSPCEGGSPAANCSCLEGLAGQRCQVPTL 1197

Qy       1080 PCEANPCLNGGTCRAAGGVSECICNARFSGQFCEVAKGLPLPLPPLLEVAVPAACACLL 1139
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1198 PCEANPCLNGGTCRAAGGVSECICNARFSGQFCEVAKGLPLPLPPLLEVAVPAACACLL 1257

Qy       1140 LLLLGLLSGILAARKRRQSEGTYSPSQQEVAGARLEMDSVLKVPPEERLI 1189
              ||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1258 LLLLGLLSGILAARKRRQSEGTYSPSQQEVAGARLEMDSVLKVPPEERLI 1307
```

Appendix C
DNA encoding SEQ ID NO: 2

```
US-10-303-685-8
; Sequence 8, Application US/10303685
; Publication No. US20030100005A1
; GENERAL INFORMATION:
;  APPLICANT: Exelixis, Inc.
;  TITLE OF INVENTION: CRBs AS MODIFIERS OF BRANCHING MORPHOGENESIS AND METHODS OF USE
;  FILE REFERENCE: EX02-125C
;  CURRENT APPLICATION NUMBER: US/10/303,685
;  CURRENT FILING DATE:  2002-11-25
;  PRIOR APPLICATION NUMBER: 60/333,368
;  PRIOR FILING DATE: 2001-11-26
;  NUMBER OF SEQ ID NOS: 17
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 8
;   LENGTH: 3786
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-10-303-685-8

Alignment Scores:
Pred. No.:              0               Length:         3786
Score:                  6808.00         Matches:        1221
Percent Similarity:     96.8%           Conservative:   0
Best Local Similarity:  96.8%           Mismatches:     3
Query Match:            98.6%           Indels:         36
DB:                     7               Gaps:           1

US-10-540-844-2 (1-1236) x US-10-303-685-8 (1-3786)

Qy          13 MetAlaLeuAlaArgProGlyThrProAspProGlnAlaLeuAlaSerValLeuLeu 32
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db           1 ATGGGCGCTGGCCAGGCCTGGGACCCCGGACCCCCAGGCCCTGGCCTCTGTCCTGCTACTG 60

Qy          33 LeuLeuTrpAlaProAlaLeuSerLeuLeuAlaGlyThrValProSerGluProProSer 52
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          61 CTGCTCTGGGCCCCTGCCCTTTCCCTCCTGGCTGGGACGGTGCCTTCAGAGCCCCCCAGT 120

Qy          53 AlaCysAlaSerAspProCysAlaProGlyThrGluCysGlnAlaThrGluSerGlyGly 72
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         121 GCCTGTGCCTCAGACCCGTGCGCTCCAGGGACCGAGTGCCAGGCTACCGAGAGTGGTGGC 180

Qy          73 TyrThrCysGlyProMetGluProArgGlyCysAlaThrGlnProCysHisHisGlyAla 92
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         181 TATACCTGTGGGCCCATGGAGCCCCGGGGCTGTGCCACCCAGCCATGCCACCACGGCGCT 240

Qy          93 LeuCysValProGlnGlyProAspProAsnGlyPheArgCysTyrCysValProGlyPhe 112
               |||||||||||||||||||||||||   |||||||||||||||||||||||||||||||
Db         241 CTGTGTGTGCCCCAGGGTCCAGATCCCACCGGCTTCCGCTGCTACTGCGTGCCGGGTTTC 300

Qy         113 GlnGlyProArgCysGluLeuAspIleAspGluCysAlaSerArgProCysHisHisGly 132
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         301 CAGGGCCCACGCTGCGAGCTGGACATCGATGAGTGTGCATCCCGGCCGTGCCACCATGGG 360
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Qy       133 AlaThrCysArgAsnLeuAlaAspArgTyrGluCysHisCysProLeuGlyTyrAlaGly 152
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       361 GCCACCTGCCGCAACCTGGCCGATCGCTACGAGTGCCATTGCCCCCTTGGCTATGCAGGC 420

Qy       153 ValThrCysGluMetGluValAspGluCysAlaSerAlaProCysLeuHisGlyGlySer 172
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       421 GTGACCTGCGAGATGGAGGTGGACGAGTGCGCCTCAGCGCCCTGCCTGCACGGGGGCTCG 480

Qy       173 CysLeuAspGlyValGlySerPheArgCysValCysAlaProGlyTyrGlyGlyThrArg 192
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       481 TGCCTGGACGGCGTGGGCTCCTTCCGCTGTGTGTGCGCGCCAGGCTACGGGGGCACCCGT 540

Qy       193 CysGlnLeuAspLeuAspGluCysGlnSerGlnProCysAlaHisGlyGlyThrCysHis 212
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       541 TGCCAGCTGGACCTCGACGAGTGCCAGAGCCAGCCGTGCGCACATGGGGGCACGTGCCAC 600

Qy       213 AspLeuValAsnGlyPheArgCysAspCysAlaGlyThrGlyTyrGluGlyThrHisCys 232
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       601 GACCTGGTCAACGGGTTCCGGTGCGACTGCGCGGGCACCGGCTACGAGGGCACGCACTGC 660

Qy       233 GluArgGluValLeuGluCysAlaSerAlaProCysGluHisAsnAlaSerCysLeuGlu 252
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       661 GAGCGGGAGGTGCTGGAGTGCGCATCGGCGCCCTGCGAGCACAACGCGTCCTGCCTCGAG 720

Qy       253 GlyLeuGlySerPheArgCysLeuCysTrpProGlyTyrSerGlyGluLeuCysGluVal 272
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       721 GGCCTCGGGAGCTTCCGCTGCCTCTGTTGGCCAGGCTACAGCGGCGAGCTGTGCGAGGTG 780

Qy       273 AspGluAspGluCysAlaSerSerProCysGlnHisGlyGlyArgCysLeuGlnArgSer 292
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       781 GACGAGGACGAGTGTGCATCGAGCCCCTGCCAGCATGGGGGCCGATGCCTGCAGCGCTCT 840

Qy       293 AspProAlaLeuTyrGlyGlyValGlnAlaAlaPheProGlyAlaPheSerPheArgHis 312
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       841 GACCCGGCCCTCTACGGGGGTGTCCAGGCCGCCTTCCCTGGCGCCTTCAGCTTCCGCCAT 900

Qy       313 AlaAlaGlyPheLeuCysHisCysProProGlyPheGlu---------------------- 325
             ||||||||||||||||||||||||||||||||||||||
Db       901 GCTGCGGGTTTCCTGTGCCACTGCCCTCCTGGCTTTGAGGGAGCCGACTGCGGTGTGGAG 960

Qy       325 ---------------------------------------------------------------- 325

Db       961 GTGGACGAGTGTGCCTCACGGCCATGCCTCAACGGAGGCCACTGCCAGGACCTGCCCAAT 1020

Qy       326 ----------------------------------GlyProThrCysGluGluAspValAsp 334
                                                 ||||||||||||||||||||||||||
Db      1021 GGCTTCCAGTGTCACTGCCCAGATGGCTACGCAGGGCCGACATGTGAGGAAGATGTGGAT 1080

Qy       335 GluCysLeuSerAspProCysLeuHisGlyGlyThrCysSerAspThrValAlaGlyTyr 354
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1081 GAATGCCTGTCGGATCCCTGCCTGCACGGCGGAACCTGCAGTGACACTGTGGCAGGCTAT 1140

Qy       355 IleCysArgCysProGluThrTrpGlyGlyArgAspCysSerValGlnLeuThrGlyCys 374
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1141 ATCTGCAGGTGCCCAGAGACCTGGGGTGGGCGCGACTGTTCTGTGCAGCTCACTGGCTGC 1200
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Qy        375 GlnGlyHisThrCysProLeuAlaAlaThrCysIleProIlePheGluSerGlyValHis 394
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1201 CAGGGCCACACCTGCCCGCTGGCTGCCACCTGCATCCCTATCTTCGAGTCTGGGGTCCAC 1260

Qy        395 SerTyrValCysHisCysProProGlyThrHisGlyProPheCysGlyGlnAsnThrThr 414
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1261 AGTTACGTCTGCCACTGCCCACCTGGTACCCATGGACCGTTCTGTGGCCAGAATACCACC 1320

Qy        415 PheSerValMetAlaGlySerProIleGlnAlaSerValProAlaGlyGlyProLeuGly 434
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1321 TTCTCTGTGATGGCTGGGAGCCCCATTCAGGCATCAGTGCCAGCTGGTGGCCCCCTGGGT 1380

Qy        435 LeuAlaLeuArgPheArgThrThrLeuProAlaGlyThrLeuAlaThrArgAsnAspThr 454
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1381 CTGGCACTGAGGTTTCGCACCACACTGCCCGCTGGGACCTTGGCCACTCGCAATGACACC 1440

Qy        455 LysGluSerLeuGluLeuAlaLeuValAlaAlaThrLeuGlnAlaThrLeuTrpSerTyr 474
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1441 AAGGAAAGCTTGGAGCTGGCATTGGTGGCAGCCACACTTCAGGCCACACTCTGGAGCTAC 1500

Qy        475 SerThrThrValLeuValLeuArgLeuProAspLeuAlaLeuAsnAspGlyHisTrpHis 494
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1501 AGCACCACTGTGCTTGTCCTGAGACTGCCGGACCTGGCCTAAACGATGGCCATTGGCAC 1560

Qy        495 GlnValGluValValLeuHisLeuAlaThrLeuGluLeuArgLeuTrpHisGluGlyCys 514
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1561 CAGGTGGAGGTTGTGCTCCATCTAGCGACCCTGGAGCTACGGCTCTGGCATGAGGGCTGC 1620

Qy        515 ProAlaArgLeuCysValAlaSerGlyProValAlaLeuAlaSerThrAlaSerAlaThr 534
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1621 CCTGCCCGGCTCTGTGTGGCCTCTGGTCCTGTGGCCCTGGCTTCCACGGCTTCGGCAACT 1680

Qy        535 ProLeuProAlaGlyIleSerSerAlaGlnLeuGlyAspAlaThrPheAlaGlyCysLeu 554
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1681 CCGCTGCCTGCCGGGATCTCCTCTGCCCAGCTGGGGGACGCGACCTTTGCAGGCTGCCTC 1740

Qy        555 GlnAspValArgValAspGlyHisLeuLeuLeuProGluAspLeuGlyGluAsnValLeu 574
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1741 CAGGACGTGCGTGTGGATGGCCACCTCCTGCTGCCTGAGGATCTCGGTGAGAACGTCCTC 1800

Qy        575 LeuGlyCysGluArgArgGluGlnCysArgProLeuProCysValHisGlyGlySerCys 594
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1801 CTGGGCTGTGAGCGCCGAGAGCAGTGCCGGCCTCTGCCTTGTGTCCACGGAGGGTCCTGT 1860

Qy        595 ValAspLeuTrpThrHisPheArgCysAspCysAlaArgProHisArgGlyProThrCys 614
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1861 GTGGATCTGTGGACTCATTTCCGTTGCGACTGTGCCCGGCCCCATAGAGGTCCCACGTGC 1920

Qy        615 AlaAspGluIleProAlaAlaThrPheGlyLeuGlyGlyAlaProSerSerAlaSerPhe 634
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1921 GCTGATGAGATTCCTGCTGCCACCTTTGGCTTGGGAGGCGCCCCAAGCTCTGCCTCCTTT 1980
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Qy       635 LeuLeuGlnGluLeuProGlyProAsnLeuThrValSerPheLeuLeuArgThrArgGlu 654
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1981 CTGCTCCAAGAGCTGCCAGGTCCCAACCTCACAGTGTCTTTCCTTCTCCGCACTCGGGAG 2040

Qy       655 SerAlaGlyLeuLeuLeuGlnPheAlaAsnAspSerAlaAlaGlyLeuThrValPheLeu 674
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2041 TCCGCTGGCCTGTTGCTCCAGTTTGCCAATGACTCCGCAGCTGGCCTAACAGTATTCCTG 2100

Qy       675 SerGluGlyArgIleArgAlaGluAlaProGlySerProAlaValValLeuProGlyArg 694
             |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2101 AGTGAGGGTCGGATCCGGGCTGAGGTGCCGGGCAGTCCTGCTGTAGTGCTCCCTGGGCGC 2160

Qy       695 TrpAspAspGlyLeuArgHisLeuValMetLeuSerPheGlyProAspGlnLeuGlnAsp 714
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2161 TGGGATGATGGGCTCCGTCACCTGGTGATGCTCAGCTTCGGGCCTGACCAGCTGCAGGAC 2220

Qy       715 LeuGlyGlnHisValHisValGlyGlyArgLeuLeuAlaAlaAspSerGlnProTrpGly 734
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2221 CTGGGGCAGCACGTGCACGTGGGTGGGAGGCTCCTTGCTGCCGACAGCCAGCCCTGGGGT 2280

Qy       735 GlyProPheArgGlyCysLeuGlnAspLeuArgLeuAspGlyCysHisLeuProPhePhe 754
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2281 GGGCCCTTCCGAGGCTGCCTCCAGGACCTGCGACTCGATGGCTGCCACCTCCCCTTCTTT 2340

Qy       755 ProLeuProLeuAspAsnSerSerGlnProSerGluLeuGlyGlyArgGlnSerTrpAsn 774
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2341 CCTCTGCCACTGGATAACTCAAGCCAGCCCAGCGAGCTCGGCGGCAGGCAGTCCTGGAAC 2400

Qy       775 LeuThrAlaGlyCysValSerGluAspMetCysSerProAspProCysPheAsnGlyGly 794
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2401 CTCACTGCGGGCTGCGTCTCCGAGGACATGTGCAGTCCTGACCCCTGTTTCAATGGTGGG 2460

Qy       795 ThrCysLeuValThrTrpAsnAspPheHisCysThrCysProAlaAsnPheThrGlyPro 814
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2461 ACTTGCCTCGTCACCTGGAATGACTTCCACTGTACCTGCCCTGCCAATTTCACGGGGCCT 2520

Qy       815 ThrCysAlaGlnGlnLeuTrpCysProGlyGlnProCysLeuProProAlaThrCysGlu 834
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2521 ACGTGTGCCCAGCAGCTGTGGTGTCCCGGCCAGCCCTGTCTCCCACCTGCCACGTGTGAG 2580

Qy       835 GluValProAspGlyPheValCysValAlaGluAlaThrPheArgGluGlyProProAla 854
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2581 GAGGTCCCTGATGGCTTTGTGTGTGTGGCGGAGGCCACGTTCCGCGAGGGTCCCCCCGCC 2640

Qy       855 AlaPheSerGlyHisAsnAlaSerSerGlyArgLeuLeuGlyGlyLeuSerLeuAlaPhe 874
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2641 GCGTTCAGCGGGCACAACGCGTCGTCAGGGCGCTTGCTCGGCGGCCTGTCGCTGGCCTTT 2700

Qy       875 ArgThrArgAspSerGluAlaTrpLeuLeuArgAlaAlaAlaGlyAlaLeuGluGlyVal 894
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2701 CGCACGCGCGACTCCGAGGCCTGGCTGCTGCGTGCCGCGGCGGGCGCCCTGGAAGGCGTG 2760

Qy       895 TrpLeuAlaValArgAsnGlySerLeuAlaGlyGlyValArgGlyGlyHisGlyLeuPro 914
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2761 TGGCTGGCGGTGCGCAATGGCTCGCTGGCGGGGGGGCGTGCGCGGAGGCCATGGCCTGCCC 2820
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Qy       915 GlyAlaValLeuProIleProGlyProArgValAlaAspGlyAlaTrpHisArgValArg 934
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2821 GGCGCTGTGCTGCCCATACCGGGGGCCGCGCGTGGCCGATGGTGCCTGGCACCGCGTGCGT 2880

Qy       935 LeuAlaMetGluArgProAlaAlaAlaThrSerArgTrpLeuLeuTrpLeuAspGlyAla 954
             |||||||||||||||||||||||||   ||||||||||||||||||||||||||||||||||
Db      2881 CTGGCCATGGAGCGCCCGGCGGCCACCACCTCGCGCTGGCTGCTGTGGCTGGATGGTGCC 2940

Qy       955 AlaThrProValAlaLeuArgGlyLeuAlaSerAspLeuGlyPheLeuGlnGlyProGly 974
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2941 GCCACCCCGGTGGCGCTGCGCGGCCTGGCCAGTGACCTGGGCTTCCTGCAGGGCCCGGGT 3000

Qy       975 AlaValArgIleLeuLeuAlaGluAsnPheThrGlyCysLeuGlyArgHisPheAlaSer 994
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3001 GCTGTGCGCATCCTGCTGGCTGAGAACTTCACCGGCTGCTTGGGCCGCCACTTCGCGTCT 3060

Qy       995 TrpProGlyThrProAlaProIleLeuGlyCysArgGlyAlaProValCysAlaProSer 1014
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3061 TGGCCTGGGACGCCGGCCCCGATCCTCGGCTGCCGGCGGCGCCGGTGTGTGCGCCCTCG 3120

Qy      1015 ProCysLeuHisAspGlyAlaCysArgAspLeuPheAspAlaPheAlaCysAlaCysGly 1034
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3121 CCCTGTCTGCACGACGGTGCCTGCCGTGACCTCTTCGACGCCTTTGCCTGCGCCTGCGGC 3180

Qy      1035 ProGlyTrpGluGlyProArgCysGluAlaHisValAspProCysHisSerAlaProCys 1054
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3181 CCGGGGTGGGAAGGCCCGCGCTGCGAAGCCCACGTCGACCCCTGTCACTCCGCCCCCTGC 3240

Qy      1055 AlaArgGlyArgCysHisThrHisProAspGlyArgPheGluCysArgCysProProGly 1074
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3241 GCCCGTGGCCGCTGTCACACGCACCCCGACGGGCCGCTTCGAGTGCCGCTGCCCGCCTGGC 3300

Qy      1075 PheGlyGlyProArgCysArgLeuProValProSerLysGluCysSerLeuAsnValThr 1094
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3301 TTCGGGGGCCCGCGCTGCAGGTTGCCTGTCCCATCCAAGGAGTGCAGCCTGAATGTCACC 3360

Qy      1095 CysLeuAspGlySerProCysGluGlyGlySerProAlaAlaAsnCysSerCysLeuGlu 1114
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3361 TGCCTCGATGGCAGCCCATGTGAGGGTGGCTCTCCCGCTGCCAACTGCAGCTGCCTGGAG 3420

Qy      1115 GlyLeuAlaGlyGlnArgCysGlnValProThrLeuProCysGluAlaAsnProCysLeu 1134
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3421 GGTCTTGCTGGCCAGAGGTGTCAGGTCCCCACTCTCCCCTGTGAAGCCAACCCCTGCTTG 3480

Qy      1135 AsnGlyGlyThrCysArgAlaAlaGlyGlyValSerGluCysIleCysAsnAlaArgPhe 1154
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3481 AATGGGGGCACCTGCCGGGCAGCTGGAGGGGTGTCTGAATGTATCTGCAATGCCAGATTC 3540

Qy      1155 SerGlyGlnPheCysGluValAlaLysGlyLeuProLeuProLeuProPheProLeuLeu 1174
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3541 TCCGGCCAGTTCTGTGAAGTGGCGAAGGGCCTGCCCCTGCCGCTGCCATTCCCACTGCTG 3600
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Qy       1175 GluValAlaValProAlaAlaCysAlaCysLeuLeuLeuLeuLeuLeuGlyLeuLeuSer 1194
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3601 GAGGTGGCCGTACCTGCAGCCTGTGCCTGCCTCCTCCTCCTCCTGGGCCTCCTTTCA 3660

Qy       1195 GlyIleLeuAlaAlaArgLysArgArgGlnSerGluGlyThrTyrSerProSerGlnGln 1214
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3661 GGGATCCTGGCAGCCCGAAAGCGCCGCCAGTCTGAGGGCACCTACAGCCCAAGCCAGCAG 3720

Qy       1215 GluValAlaGlyAlaArgLeuGluMetAspSerValLeuLysValProProGluGluArg 1234
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3721 GAGGTGGCTGGGGCCCGGCTGGAGATGGACAGTGTCCTCAAGGTGCCACCGGAGGAGAGA 3780

Qy       1235 LeuIle 1236
             ||||||
Db       3781 CTCATC 3786
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Appendix D
DNA encoding SEQ ID NO: 4

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US-10-303-685-8
; Sequence 8, Application US/10303685
; Publication No. US20030100005A1
; GENERAL INFORMATION:
;  APPLICANT: Exelixis, Inc.
;  TITLE OF INVENTION: CREs AS MODIFIERS OF BRANCHING MORPHOGENESIS AND METHODS OF USE
;  FILE REFERENCE: EX02-125C
;  CURRENT APPLICATION NUMBER: US/10/303,685
;  CURRENT FILING DATE:  2002-11-25
;  PRIOR APPLICATION NUMBER: 60/333,388
;  PRIOR FILING DATE: 2001-11-26
;  NUMBER OF SEQ ID NOS: 17
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 8
;  LENGTH: 3786
;  TYPE: DNA
;  ORGANISM: Homo sapiens
US-10-303-685-8

Alignment Scores:
Pred. No.:              0               Length:         3786
Score:                  6635.00         Matches:        1186
Percent Similarity:     96.7%           Conservative:   0
Best Local Similarity:  96.7%           Mismatches:     3
Query Match:            99.4%           Indels:         38
DB:                     7               Gaps:           1

US-10-540-844-4 (1-1189) x US-10-303-685-8 (1-3786)

Qy          1 SerGluProProSerAlaCysAlaSerAspProCysAlaProGlyThrGluCysGlnAla 20
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        106 TCAGAGCCCCCCAGTGCCTGTGCCTCAGACCCGTGCGCTCCAGGGACCGAGTGCCAGGCT 165

Qy         21 ThrGluSerGlyGlyTyrThrCysGlyProMetGluProArgGlyCysAlaThrGlnPro 40
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        166 ACCGAGAGTGGTGGCTATACCTGTGGGCCCATGGAGCCCCGGGGCTGTGCCACCCAGCCA 225

Qy         41 CysHisHisGlyAlaLeuCysValProGlnGlyProAspProAsnGlyPheArgCysTyr 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        226 TGCCACCACGGCGCTCTGTGTGTGCCCCAGGGTCCAGATCCCACCGGCTTCCGCTGCTAC 285

Qy         61 CysValProGlyPheGlnGlyProArgCysGluLeuAspIleAspGluCysAlaSerArg 80
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        286 TGCGTGCCGGGTTTCCAGGGCCCACGCTGCGAGCTGGACATCGATGAGTGTGCATCCCGG 345

Qy         81 ProCysHisHisGlyAlaThrCysArgAsnLeuAlaAspArgTyrGluCysHisCysPro 100
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        346 CCGTGCCACCATGGGGCCACCTGCCGCAACCTGGCCGATCGCTACGAGTGCCATTGCCCC 405

Qy        101 LeuGlyTyrAlaGlyValThrCysGluMetGluValAspGluCysAlaSerAlaProCys 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        406 CTTGGCTATGCAGGCGTGACCTGCGAGATGGAGGTGGACGAGTGCGCCTCAGCGCCCTGC 465
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Qy       121 LeuHisGlyGlySerCysLeuAspGlyValGlySerPheArgCysValCysAlaProGly 140
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       466 CTGCACGGGGGCTCGTGCCTGGACGGCGTGGGCTCCTTCCGCTGTGTGTGCGCGCCAGGC 525

Qy       141 TyrGlyGlyThrArgCysGlnLeuAspLeuAspGluCysGlnSerGlnProCysAlaHis 160
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       526 TACGGGGGCACCCGTTGCCAGCTGGACCTCGACGAGTGCCAGAGCCAGCCGTGCGCACAT 585

Qy       161 GlyGlyThrCysHisAspLeuValAsnGlyPheArgCysAspCysAlaGlyThrGlyTyr 180
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       586 GGGGGCACGTGCCACGACCTGGTCAACGGGTTCCGGTGCGACTGCGCGGGCACCGGCTAC 645

Qy       181 GluGlyThrHisCysGluArgGluValLeuGluCysAlaSerAlaProCysGluHisAsn 200
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       646 GAGGGCACGCACTGCGAGCGGGAGGTGCTGGAGTGCGCATCGGCGCCCTGCGAGCACAAC 705

Qy       201 AlaSerCysLeuGluGlyLeuGlySerPheArgCysLeuCysTrpProGlyTyrSerGly 220
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       706 GCGTCCTGCCTCGAGGGCCTCGGGAGCTTCCGCTGCCTCTGTTGGCCAGGCTACAGCGGC 765

Qy       221 GluLeuCysGluValAspGluAspGluCysAlaSerSerProCysGlnHisGlyGlyArg 240
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       766 GAGCTGTGCGAGGTGGACGAGGACGAGTGTGCATCGAGCCCCTGCCAGCATGGGGGCCGA 825

Qy       241 CysLeuGlnArgSerAspProAlaLeuTyrGlyGlyValGlnAlaAlaPheProGlyAla 260
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       826 TGCCTGCAGCGCTCTGACCCGGCCCTCTACGGGGGTGTCCAGGCCGCCTTCCCTGGCGCC 885

Qy       261 PheSerPheArgHisAlaAlaGlyPheLeuCysHisCysProProGlyPheGlu------ 278
            ||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       886 TTCAGCTTCCGCCATGCTGCGGGGTTTCCTGTGCCACTGCCCTCCTGGCTTTGAGGGAGCC 945

Qy       278 ------------------------------------------------------------ 278

Db       946 GACTGCGGTGTGGAGGTGGACGAGTGTGCCTCACGGCCATGCCTCAACGGAGGCCACTGC 1005

Qy       279 ----------------------------------------------------GlyProThrCys 282
                                                                    ||||||||||||
Db      1006 CAGGACCTGCCCAATGGCTTCCAGTGTCACTGCCCAGATGGCTACGCAGGGCCGACATGT 1065

Qy       283 GluGluAspValAspGluCysLeuSerAspProCysLeuHisGlyGlyThrCysSerAsp 302
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1066 GAGGAAGATGTGGATGAATGCCTGTCGGATCCCTGCCTGCACGGCGGAACCTGCAGTGAC 1125

Qy       303 ThrValAlaGlyTyrIleCysArgCysProGluThrTrpGlyGlyArgAspCysSerVal 322
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1126 ACTGTGGCAGGCTATATCTGCAGGTGCCCAGAGACCTGGGGTGGGCGCGACTGTTCTGTG 1185

Qy       323 GlnLeuThrGlyCysGlnGlyHisThrCysProLeuAlaAlaThrCysIleProIlePhe 342
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1186 CAGCTCACTGGCTGCCAGGGCCACACCTGCCCGCTGGCTGCCACCTGCATCCCTATCTTC 1245

Qy       343 GluSerGlyValHisSerTyrValCysHisCysProProGlyThrHisGlyProPheCys 362
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1246 GAGTCTGGGGTCCACAGTTACGTCTGCCACTGCCCACCTGGTACCCATGGACCGTTCTGT 1305
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Qy        363 GlyGlnAsnThrThrPheSerValMetAlaGlySerProIleGlnAlaSerValProAla 382
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1305 GGCCAGAATACCACCTTCTCTGTGATGGCTGGGAGCCCCATTCAGGCATCAGTGCCAGCT 1365

Qy        383 GlyGlyProLeuGlyLeuAlaLeuArgPheArgThrThrLeuProAlaGlyThrLeuAla 402
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1366 GGTGGCCCCCTGGGTCTGGCACTGAGGTTTCGCACCACACTGCCCGCTGGGACCTTGGCC 1425

Qy        403 ThrArgAsnAspThrLysGluSerLeuGluLeuAlaLeuValAlaAlaThrLeuGlnAla 422
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1426 ACTCGCAATGACACCAAGGAAAGCTTGGAGCTGGCATTGGTGGCAGCCACACTTCAGGCC 1485

Qy        423 ThrLeuTrpSerTyrSerThrThrValLeuValLeuArgLeuProAspLeuAlaLeuAsn 442
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1486 ACACTCTGGAGCTACAGCACCACTGTGCTTGTCCTGAGACTGCCGGACCTGGCCCTAAAC 1545

Qy        443 AspGlyHisTrpHisGlnValGluValValLeuHisLeuAlaThrLeuGluLeuArgLeu 462
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1546 GATGGCCATTGGCACCAGGTGGAGGTTGTGCTCCATCTAGCGACCCTGGAGCTACGGCTC 1605

Qy        463 TrpHisGluGlyCysProAlaArgLeuCysValAlaSerGlyProValAlaLeuAlaSer 482
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1606 TGGCATGAGGGCTGCCCTGCCCGGCTCTGTGTGGCCTCTGGTCCTGTGGCCCTGGCTTCC 1665

Qy        483 ThrAlaSerAlaThrProLeuProAlaGlyIleSerSerAlaGlnLeuGlyAspAlaThr 502
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1666 ACGGCTTCGGCAACTCCGCTGCCTGCCGGGATCTCCTCTGCCCAGCTGGGGGACGCGACC 1725

Qy        503 PheAlaGlyCysLeuGlnAspValArgValAspGlyHisLeuLeuLeuProGluAspLeu 522
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1726 TTTGCAGGCTGCCTCCAGGACGTGCGTGTGGATGGCCACCTCCTGCTGCCTGAGGATCTC 1785

Qy        523 GlyGluAsnValLeuLeuGlyCysGluArgArgGluGlnCysArgProLeuProCysVal 542
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1786 GGTGAGAACGTCCTCCTGGGCTGTGAGCGCCGAGAGCAGTGCCGGCCTCTGCCTTGTGTC 1845

Qy        543 HisGlySerCysValAspLeuTrpThrHisPheArgCysAspCysAlaArgProHis 562
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1846 CACGGAGGGTCCTGTGTGGATCTGTGGACTCATTTCCGTTGCGACTGTGCCCGGCCCCAT 1905

Qy        563 ArgGlyProThrCysAlaAspGluIleProAlaAlaThrPheGlyLeuGlyGlyAlaPro 582
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1906 AGAGGTCCCACGTGCGCTGATGAGATTCCTGCTGCCACCTTTGGCTTGGGAGGCGCCCCA 1965

Qy        583 SerSerAlaSerPheLeuLeuGlnGluLeuProGlyProAsnLeuThrValSerPheLeu 602
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1966 AGCTCTGCCTCCTTTCTGCTCCAAGAGCTGCCAGGTCCCAACCTCACAGTGTCTTTCCTT 2025

Qy        603 LeuArgThrArgGluSerAlaGlyLeuLeuLeuGlnPheAlaAsnAspSerAlaAlaGly 622
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2026 CTCCGCACTCGGGAGTCCGCTGGCCTGTTGCTCCAGTTTGCCAATGACTCCGCAGCTGGC 2085
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Qy        623 LeuThrValPheLeuSerGluGlyArgIleArgAlaGluAlaProGlySerProAlaVal 642
              |||||||||||||||||||||||||||||||||||||||    ||||||||||||||||||
Db       2086 CTAACAGTATTCCTGAGTGAGGGTCGGATCCGGGCTGAGGTGCCGGGCAGTCCTGCTGTA 2145

Qy        643 ValLeuProGlyArgTrpAspAspGlyLeuArgHisLeuValMetLeuSerPheGlyPro 662
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2146 GTGCTCCCTGGGCGCTGGGATGATGGGCTCCGTCACCTGGTGATGCTCAGCTTCGGGCCT 2205

Qy        663 AspGlnLeuGlnAspLeuGlyGlnHisValHisValGlyGlyArgLeuLeuAlaAlaAsp 682
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Db       2206 GACCAGCTGCAGGACCTGGGGCAGCACGTGCACGTGGGTGGGAGGCTCCTTGCTGCCGAC 2265

Qy        683 SerGlnProTrpGlyGlyProPheArgGlyCysLeuGlnAspLeuArgLeuAspGlyCys 702
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2266 AGCCAGCCCTGGGGTGGGCCCTTCCGAGGCTGCCTCCAGGACCTGCGACTCGATGGCTGC 2325

Qy        703 HisLeuProPheProProLeuProLeuAspAsnSerSerGlnProSerGlyLeuGlyGly 722
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2326 CACCTCCCCTTCTTTCCTCTGCCACTGGATAACTCAAGCCAGCCCAGCGAGCTCGGCGGC 2385

Qy        723 ArgGlnSerTrpAsnLeuThrAlaGlyCysValSerGluAspMetCysSerProAspPro 742
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Db       2386 AGGCAGTCCTGGAACCTCACTGCGGGCTGCGTCTCCGAGGACATGTGCAGTCCTGACCCC 2445

Qy        743 CysPheAsnGlyGlyThrCysLeuValThrTrpAsnAspPheHisCysThrCysProAla 762
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2446 TGTTTCAATGGTGGGACTTGCCTCGTCACCTGGAATGACTTCCACTGTACCTGCCCTGCC 2505

Qy        763 AsnPheThrGlyProThrCysAlaGlnGlnLeuTrpCysProGlyGlnProCysLeuPro 782
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2506 AATTTCACGGGGCCTACGTGTGCCCAGCAGCTGTGGTGTCCCGGCCAGCCCTGTCTCCCA 2565

Qy        783 ProAlaThrCysGluGluValProAspGlyPheValCysValAlaGluAlaThrPheArg 802
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2566 CCTGCCACGTGTGAGGAGGTCCCTGATGGCTTTGTGTGTGTGGCGGAGGCCACGTTCCGC 2625

Qy        803 GluGlyProProAlaAlaPheSerGlyHisAsnAlaSerSerGlyArgLeuLeuGlyGly 822
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2626 GAGGGTCCCCCCGCCGCGTTCAGCGGGCACAACGCGTCGTCAGGGCGCTTGCTCGGCGGC 2685

Qy        823 LeuSerLeuAlaPheArgThrArgAspSerGluAlaTrpLeuLeuArgAlaAlaAlaGly 842
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Db       2686 CTGTCGCTGGCCTTTCGCACGCGCGACTCCGAGGCCTGGCTGCTGCGTGCCGCGGCGGGC 2745

Qy        843 AlaLeuGluGlyValTrpLeuAlaValArgAsnGlySerLeuAlaGlyGlyValArgGly 862
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2746 GCCCTGGAAGGCGTGTGGCTGGCGGTGCGCAATGGCTCGCTGGCGGGGGGCGTGCGCGGA 2805

Qy        863 GlyHisGlyLeuProGlyAlaValLeuProIleProGlyProArgValAlaAspGlyAla 882
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2806 GGCCATGGCCTGCCCGGCGCTGTGCTGCCCATACCGGGGCCGCGCTGGCCGATGGTGCC 2865

Qy        883 TrpHisArgValArgLeuAlaMetGluArgProAlaAlaAlaThrSerArgTrpLeuLeu 902
              ||||||||||||||||||||||||||||||||||||||    ||||||||||||||||||
Db       2866 TGGCACCGCGTGCGTCTGGCCATGGAGCGCCCGGCGGCCACCACCTCGCGCTGGCTGCTG 2925
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Qy       903 TrpLeuAspGlyAlaAlaThrProValAlaLeuArgGlyLeuAlaSerAspLeuGlyPhe 922
Db      2926 TGGCTGGATGGTGCCGCCACCCCGGTGGCGCTGCGCGGCCTGGCCAGTGACCTGGGCTTC 2985

Qy       923 LeuGlnGlyProGlyAlaValArgIleLeuLeuAlaGluAsnPheThrGlyCysLeuGly 942
Db      2986 CTGCAGGGCCCGGGTGCTGTGCGCATCCTGCTGGCTGAGAACTTCACCGGCTGCTTGGGC 3045

Qy       943 ArgHisPheAlaSerTrpProGlyThrProAlaProIleLeuGlyCysArgGlyAlaPro 962
Db      3046 CGCCACTTCGCGTCTTGGCCTGGGACGCCGGCCCCGATCCTCGGCTGCCGCGGCGCCC 3105

Qy       963 ValCysAlaProSerProCysLeuHisAspGlyAlaCysArgAspLeuPheAspAlaPhe 982
Db      3106 GTGTGTGCGCCCTCGCCCTGTCTGCACGACGGTGCCTGCCGTGACCTCTTCGACGCCTTT 3165

Qy       983 AlaCysAlaCysGlyProGlyTrpGluGlyProArgCysGluAlaHisValAspProCys 1002
Db      3166 GCCTGCGCCTGCGGCCCGGGGTGGGAAGGCCCGCGCTGCGAAGCCCACGTCGACCCCTGT 3225

Qy      1003 HisSerAlaProCysAlaArgGlyArgCysHisThrHisProAspGlyArgPheGluCys 1022
Db      3226 CACTCCGCCCCCTGCGCCCGTGGCCGCTGTCACACGCACCCCGACGGCCGCTTCGAGTGC 3285

Qy      1023 ArgCysProProGlyPheGlyGlyProArgCysArgLeuProValProSerLysGluCys 1042
Db      3286 CGCTGCCCGCCTGGCTTCGGGGGCCCCGGCTGCAGGTTGCCTGTCCCATCCAAGGAGTGC 3345

Qy      1043 SerLeuAsnValThrCysLeuAspGlySerProCysGluGlyGlySerProAlaAlaAsn 1062
Db      3346 AGCCTGAATGTCACCTGCCTCGATGGCAGCCCATGTGAGGGTGGCTCTCCCGCTGCCAAC 3405

Qy      1063 CysSerCysLeuGluGlyLeuAlaGlyGlnArgCysGlnValProThrLeuProCysGlu 1082
Db      3406 TGCAGCTGCCTGGAGGGTCTTGCTGGCCAGAGGTGTCAGGTCCCCACTCTCCCCTGTGAA 3465

Qy      1083 AlaAsnProCysLeuAsnGlyGlyThrCysArgAlaAlaGlyGlyValSerGluCysIle 1102
Db      3466 GCCAACCCCTGCTTGAATGGGGGCACCTGCCGGGCAGCTGGAGGGGTGTCTGAATGTATC 3525

Qy      1103 CysAsnAlaArgPheSerGlyGlnPheCysGluValAlaLysGlyLeuProLeuProLeu 1122
Db      3526 TGCAATGCCAGATTCTCCGGCCAGTTCTGTGAAGTGGCGAAGGGCCTGCCCCTGCCGCTG 3585

Qy      1123 ProPheProLeuLeuGluValAlaValProAlaAlaCysAlaCysLeuLeuLeuLeu 1142
Db      3586 CCATTCCCACTGCTGGAGGTGGCCGTACCTGCAGCCTGTGCCTGCCTCCTCCTCCTC 3645

Qy      1143 LeuGlyLeuLeuSerGlyIleLeuAlaAlaArgLysArgArgGlnSerGluGlyThrTyr 1162
Db      3646 CTGGGCCTCCTTTCAGGGATCCTGGCAGCCCGAAAGCGCCGCCAGTCTGAGGGCACCTAC 3705

Qy      1163 SerProSerGlnGlnGluValAlaGlyAlaArgLeuGluMetAspSerValLeuLysVal 1182
Db      3706 AGCCCAAGCCAGCAGGAGGTGGCTGGGGCCCGGCTGGAGATGGACAGTGTCCTCAAGGTG 3765

Qy      1183 ProProGluGluArgLeuIle 1189
Db      3766 CCACCGGAGGAGAGACTCATC 3786
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